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IRRADIATION PNEUMONITIS

Report of a Case

THEODORE O. ALEXANDER, M.D.[1]

Submitted for publication September 5, 1944

The following report describes a case of Hodgkin's disease which was treated by irradiation. It is of interest because the patient did not die from Hodgkin's disease or from anemia, but developed terminally a marked pneumonitis which was most probably due to the irradiation he received.

J. C., (Unit #160687), a 52 year old white married farmer, was admitted to the medical wards of the Johns Hopkins Hospital for the first time on January 14, 1939, complaining of cough and swelling of the neck. His illness had begun gradually about seven months previously with a feeling of fatigue and a sensation of tightness in the throat which in time was accompanied by some dysphagia. He then noticed small growths at the base of his neck just above the clavicles. Shortly after, he developed a cough and some shortness of breath. The cough was paroxysmal and productive occasionally of small amounts of blood. At the time of admission he coughed about one cupful of sputum per day. These paroxysms of coughing became so severe in time as to cause the patient to seek medical advice. More recently, he also complained of occasional pains in the chest. There had been a weight loss of fourteen pounds in the six months previous to admission. The past history was not pertinent.

Physical examination: temperature 99.6°F., pulse 106, respirations 22. The patient was a well-developed man, 5 ft. 6 inches in height, who displayed frequent paroxysms of a brassy, non-productive cough lasting from five to ten minutes. Tender glands were felt in each supraclavicular fossa, those on the left being matted and hard, whereas a single gland on the right was not as hard and was more freely movable. Several tender glands were felt in the left axilla. The lungs showed dullness to percussion above the second interspace anteriorly and above the fifth thoracic spine posteriorly on the left. Breath sounds

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over this area were harsh but no râles were heard. Examination of the remaining portions of the lungs yielded nothing of value. There was increased dullness retromanubrially and at the base of the heart. Cardiac dullness measured 10.5 cm. to the left of the midline in the fifth interspace and 5.5 cm. to the right of the midline in the fourth interspace. The rate was regular; no murmurs were heard. The

FIG. 1. ROENTGENOGRAM TAKEN 1/21/39, AT ONSET OF TREATMENT

There is widening of the mediastinal shadow with slight parenchymal infiltration bilaterally.

blood pressure was 120/70 in the left arm and 120/68 in the right arm. The abdomen was full and the liver and spleen were not felt. The prostate was moderately enlarged. Neurologic examination was negative.

The patient remained in the hospital for seventeen days. On the fourth day of admission, biopsy of a supraclavicular lymph node showed typical Hodgkin's tissue. A roentgenogram of the chest showed moderate widening of the mediastinum due to enlargement of

the lymph nodes and slight infiltration extending into the lung tissues adjacent to the hila, which was more marked on the left side (Fig. 1). A bronchoscopic examination showed partial obstruction of the trachea about one inch above the bifurcation. Irradiation was commenced and was continued for two weeks after his discharge on February 1 (Table 1). The patient was much improved and a roent-

FIG. 2. ROENTGENOGRAM TAKEN 2/6/39, SIXTEEN DAYS AFTER THE ONSET OF IRRADIATION, SHOWING SOME DECREASE IN THE SIZE OF THE MEDIASTINAL SHADOW

genogram of his chest after discharge showed a definite decrease in the mediastinal shadow and the hilar infiltration (Fig. 2).

He was subsequently admitted to the hospital on four other occasions for treatment and was seen frequently in the intervening periods in the X-Ray Therapy Department for the same purpose (Table 1).

On March 11, he was admitted to the hospital complaining of severe, continuous pain in the right flank which was exaggerated by

motion. Urine cultures, intravenous pyelography and roentgenograms of the spine failed to reveal the cause of this pain. He was discharged eight days later, somewhat improved.

TABLE I

Irradiation Given to Patient with Hodgkin's Disease

Factors: 200 P.K.V., 20 M.A., 50 cm. S.T.D., Thoraeus filter = 2 mm. copper plus 1 mm. aluninum.

DATE	TREATMENTS	FIELD	PORTAL	"R" IN AIR
			cm.	
1/21/39 to 3/1/39	10	*Anterior mediastinum	10 x 20	1,050
	10	*Posterior mediastinum	10 x 20	1,050
2/10/39 to 2/14/39	4	Left cervical	10 x 10	840
	4	Right cervical	10 x 10	840
4/3/39 to 4/6/39	4	Right inguinal	10 x 10	620
	4	Left inguinal	10 x 10	620
4/17/39 to 4/22/39	5	Right supraclavicular	15 x 15	1,000
	5	Left supraclavicular	15 x 15	1,000
4/26/39 to 5/4/39	4	*Anterior mediastinum	10 x 20	420
	4	*Posterior mediastinum	10 x 20	420
5/1/39 to 5/4/39	5	Left cervical	15 x 15	970
6/26/39 to 7/5/39	8	Right lumbar	15 x 15	800
7/6/39 to 7/10/39	4	Lower right thorax post.	15 x 15	400
7/31/39 to 8/17/39	10	Posterior mediastinum	15 x 15	2,018
	9	Anterior mediastinum	20 x 20	1,818
9/22/39 to 9/28/39	3	Posterior mediastinum	20 x 20	243
	3	Posterior lumbar	20 x 20	243

* Lung fields shielded.

On April 20 he was again admitted to the hospital after coughing up two clots of blood. This episode followed a rise in temperature to 101°F. after irradiation of the neck. The sputum remained blood streaked for several days. Roentgenograms of the chest made during this time showed more pronounced infiltration in the hilar regions.

He stayed in the hospital two weeks. On the third day he again coughed up two clots of blood. No further hemoptysis was noted, however.

On June 6 it was noted that pigmentation of the skin of the neck had developed, more marked on the left side. This was attributed to the irradiation he had received in this region.

FIG. 3. ROENTGENOGRAM TAKEN 8/14/39, DURING A COURSE OF 3836R TO THE MEDIASTINUM

There is again widening of the mediastinal shadow

A recurrence of the attacks of pain in the right flank resulted in his re-admission to the hospital on June 20. Intravenous pyelograms and urine cultures again were negative, but roentgenograms of the lumbar spine now showed destructive lesions in the lower thoracic and upper lumbar vertebrae. These most probably represented metastases. He was discharged July 10, and in the following weeks complained of anorexia, nocturnal cough and of some difficulty in breathing. On August 1, he was started on a course of irradiation

to his mediastinum during which 3836r were administered over a period of seventeen days (Table I). The lung fields were not shielded. Roentgen examination during this time showed additional widening of the mediastinum and slight infiltration of the lung tissues adjacent to the hilar regions (Fig. 3).

Increasing shortness of breath for ten days brought him to the hospital for the final admission on September 19, 1939. As he now

FIG. 4. ROENTGENOGRAM TAKEN 9/20/39, EIGHT DAYS BEFORE DEATH
There is dense infiltration in both bases, extending in less degree to the upper lung fields

explained, "I just don't have enough room in my chest for air." He had had some cough in the past few nights which was not productive of blood. There had been no chest pain. The temperature was 100°F., pulse 88. Blood pressure 85/60 in the left arm and 110/65 in the right arm. The respirations were 30 per minute, shallow and were without stridor. He was quite unable to take a deep breath. There was slight cyanosis of the face and lips, but there was no venous

engorgement. Clinically, there was dullness to percussion of the left base, slight elevation and poor excursion of the left diaphragm and an area of increased breath sounds close to the spine which suggested atelectasis. The findings on the right side were confined to some dullness over the right base. Roentgenograms of the chest showed infiltration of about the lower two thirds of each lung which became very dense in the region of either base (Fig. 4). The vital capacity was 700 and 800 cc. of air on two occasions. While on the ward, deep therapy was begun to the posterior mediastinum and to the lumbar regions. The pulse rose to 108 per minute and exhibited frequent extrasystoles. Respirations became more shallow and rapid and rose, within the last few days, to 40 per minute. He died on September 28, 1939, eight days after admission.

Various laboratory procedures carried out in the hospital showed negative results with the exception of the roentgenogram of the chest. The red blood cells varied between 5,510,000 and 4,060,000 and the white blood cells between 19,800 and 3,200. Differential counts were not significant.

At autopsy (# 16584) the relevant *gross findings* in the chest were as follows:

There was no excess fluid in either pleural cavity. The tracheal lymph nodes were discrete, slightly enlarged, measuring 10 x 4 mm. and were anthracotic. They did not compress the trachea.

The pericardial cavity contained no excess fluid. The parietal pericardium was thickened, measuring to 1.5 cm. and was bound to the anterior portion of the upper lobe on the left. It consisted mostly of scar tissue in which were small islands of fat, together with several more yellow foci, the identity of which were not clear at the time.

Both the right and the left sides of the heart were dilated, more so the right. This organ weighed 440 grams and the right ventricle was slightly hypertrophied.

The left lung externally was smooth, save for dense fibrous adhesions binding the apical visceral and parietal pleurae. Large areas in both the upper and lower lobes appeared consolidated. Within these, there were pearly, grayish-yellow areas of infiltration. The lymph nodes at the hilum were of normal size and there was no compression of the bronchi.

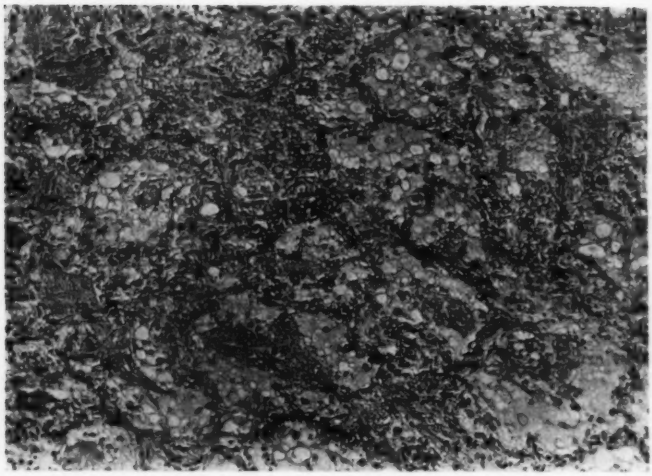

FIG. 5. SECTION OF THE RIGHT LOWER LOBE SHOWING AN EXUDATE COMPOSED OF EDEMA FLUID, FEW RED AND WHITE CELLS, FIBRIN AND SOME FIBRIN-HYALIN MEMBRANES

There are foci of organization of this exudate. × 50

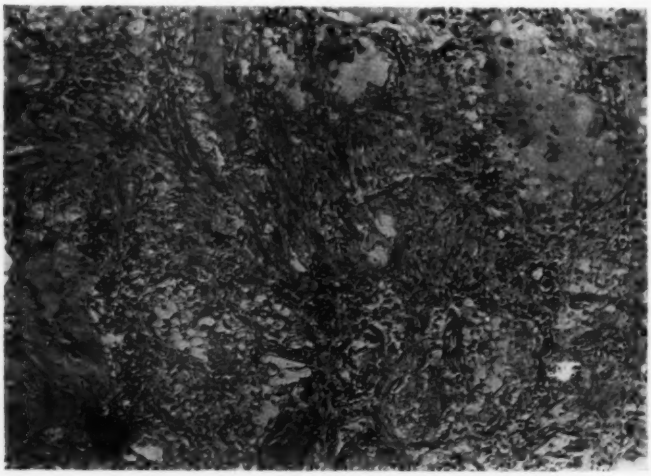

FIG. 6. RIGHT LOWER LOBE SHOWING ORGANIZATION OF THE EXUDATE. × 50

The right lung pleura was delicate, smooth and non-adherent. On section this lung, too, showed consolidated areas with the same type of grayish-yellow infiltration. The changes here were almost as widespread as those in the left lung. The bronchial lymph nodes were normal in size.

Microscopic sections showed thickening and scarring of the pericardium with a few microscopic foci of lymphocytes and Dorothy Reed cells. Moderate, diffuse fibrosis was evident in sections of the left ventricle.

Sections of both lungs showed large groups of involved alveoli between which the tissue appeared unaffected by the irradiation, showing little but emphysema. Within these involved areas a few alveoli contained edema, a few leucocytes and red blood cells. Many alveoli contained a pink-staining fibrinous material which in places was condensed at the periphery to form a fibrinous, hyaline membrane. Various stages of organization of this exudate were evident, being so massive in areas as to obliterate the alveoli. The epithelium lining some of the alveoli was swollen and had in places desquamated into the adjacent air-containing spaces. A few, fat laden macrophages were dispersed throughout. Appropriate stains revealed no bacteria. Large, deep-staining Dorothy Reed cells were seen in minute foci in the bronchial lymph nodes. No evidence of Hodgkin's tissue in the lungs was found on examination of several sections.

DISCUSSION

The characteristic pulmonary lesions due to over-irradiation have been produced in experimental animals by Davis (1) and have been described by McIntosh and Spitz (2) and by Warren and Spencer (3). The lesions found in the lungs of this patient were similar to those described by these authors.

Because of the symptoms arising from the persistently enlarged mediastinal glands and possibly from infiltration of the lungs with Hodgkin's tissue, 3836r were administered to the mediastinum late in the course of his illness without shielding the lungs. 2018r had been given through a 15 x 15 cm. portal to the posterior mediastinum and 1818r through a 20 x 20 cm. portal to the anterior mediastinum. This course of therapy ended about six weeks before the patient expired.

A few weeks later he developed severe shortness of breath with slight cyanosis and, in a roentgenogram taken eight days before his death, a definite extensive pneumonitis first appeared. Thus, in the nine months from the time therapy was started to the time these changes appeared in his lungs, he had received a total of 6776r to the mediastinum. This amount of irradiation was sufficient to produce in this man a typical irradiation pneumonitis.

SUMMARY

A case of Hodgkin's disease treated by irradiation is described. It is of interest because the patient developed marked respiratory symptoms shortly after a course of irradiation to the mediastinum where the adjacent lung tissues necessarily were not shielded. Roentgenograms at this time showed an extensive pneumonitis. At autopsy, the lungs showed lesions similar to those produced experimentally by over-irradiation. A patchy exudate composed of edema fluid, a few red and white cells, fibrin, and fibrinous-hyaline membrane was found involving the greater portion of each lung. There was widespread organization of this exudate. A few minute, microscopic foci of Hodgkin's tissue were found in the bronchial lymph nodes and in the pericardium. No Hodgkin's tissue was found in the lungs.[2]

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[2] The author wishes to express his thanks to Dr. S. S. Blackman of the Department of Pathology, The Johns Hopkins Hospital, for his assistance.

STUDIES ON FRACTURE CONVALESCENCE

II. The Influence of Diet on Post-traumatic Nitrogen Deficit Exhibited by Fracture Patients

JOHN EAGER HOWARD, M.D., JANE WINTERNITZ, PH.D., WILLIAM PARSON, M.D., ROY S. BIGHAM, JR., M.D., AND HARRY EISENBERG*

In a previous communication (1) dealing with the nitrogen metabolism of patients convalescent from fractures of large bones of the lower limbs, it was reported that large losses of body nitrogen were incurred. Skeletal operations were followed by similar, though much smaller, nitrogen losses. These findings were confirmatory to observations made on similar patients by Cuthbertson and his colleagues. It was found that, in the fracture cases, even after nitrogen equilibrium was regained (which required an average of 35 days in these patients), repletion of the lost nitrogen took place at a very slow rate (1). Some of the factors which might be relevant to the nitrogen metabolism in these patients were discussed, such as the effects of immobilization due to bed rest, atrophy of disuse, sulfonamide compounds, anesthesia, fever and infections. The present report attempts to evaluate the rôle played by diet, especially the protein intake, in the magnitude of the nitrogen losses suffered by these same patients. The methods of collection and analyses employed in these studies have been given in detail (1). Stool nitrogen was estimated as 10% of ingested nitrogen in all but two cases of this series. In these two cases the stool nitrogen was determined throughout the experiment and was found to be exceedingly close to the calculated value.

In evaluating the rôle of dietary protein and total calories, it seemed important that variations in size of the patients be given consideration. The variable factor of size was eliminated by introducing a correction factor based on the surface area of the subject, calculated from the height-weight tables of Dubois (2). All metabolic data were multiplied

* From the Department of Medicine of the Johns Hopkins University and the Johns Hopkins Hospital.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Johns Hopkins University.

by $\frac{1.73}{\text{surface area of subject (in sq.m.)}}$, and were thereby expressed in terms of an "average man" weighing 60 Kg., 175 cm. in height, whose surface area is 1.73 sq. meters.

We were unable to find in the literature any suitable data from which to derive the *expected* amount of nitrogen that might be lost or retained from a given dietary intake at bed rest. It was decided to postulate such figures, and a graph (Fig. I) was made on the following assumptions:

(1) An average man, weighing 60 kilos and with a height of 175 cm., has a surface area of 1.73 sq.m.

(2) The expenditure of energy of an adult lying still but awake is 1.10 calories per kilo per hour (3), i.e. 26.4 calories per kilo per 24 hours, or approximately 1600 calories per day per 1.73 sq.m.

(3) For a normal adult fed adequate calories an allowance of 1 gm. protein per kilo was considered liberal and somewhat more than enough to maintain nitrogen equilibrium. For an average man such an allowance would be 60 gm. protein per day or 10 gm. nitrogen/1.73 sq.m./24 hrs.

Thus from 1, 2 and 3 we should expect a normal healthy man to be in nitrogen equilibrium at bed rest if he were provided a diet containing 10 gm. nitrogen and 1600 calories/1.73 sq.m./24 hours. We have subsequently studied the nitrogen metabolism of several healthy vigorous patients for 5-day periods at bed rest before operation and have found that, when fed 10 gm. nitrogen and 1600 calories/1.73 sq.m., these patients were in negative nitrogen balance from .5 to 2 gm. per day, with an average of 1.2 gm.* This tendency to small nitrogen loss exhibited by healthy vigorous patients when put to bed is under careful investigation by Keys (4).

There are available the data of Benedict (5) that, over a 31-day period of complete starvation save for water, with minimal activity, his subject excreted an average of 8.6 gm. nitrogen in the urine/24 hours/1.73 sq.m. surface area. A healthy male medical student

* It is of interest and, perhaps of considerable importance that a few patients so far studied preoperatively, who did *not* respond to operation with the expected nitrogen catabolic increases, did not show nitrogen losses preoperatively when fed according to this formula.

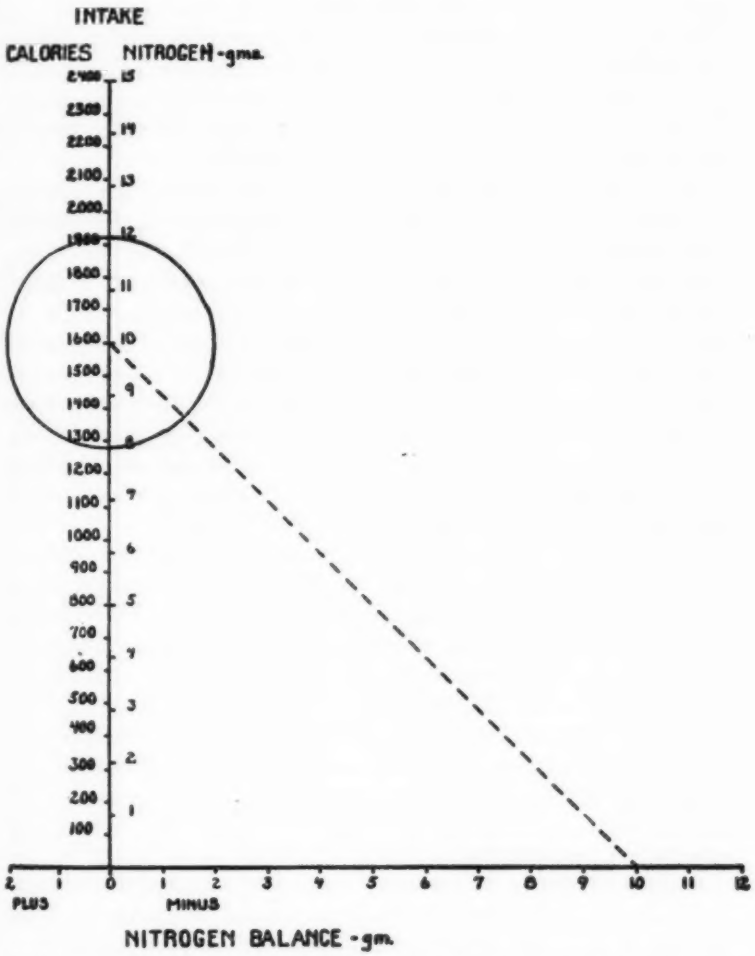

FIG. 1. RELATION BETWEEN EXPECTED NITROGEN BALANCE AND NITROGEN INTAKE

(C. W.) studied in this clinic, when undergoing a 3-day fast except for water, with minimal activity (sitting in a chair; lavoratory privileges) excreted an average of 11.3 gm./24 hours/1.73 sq.m. From these

figures a prediction has been made that, without food, at bed rest and with slight activity of turning in bed, etc., a previously healthy, vigorous person will lose approximately 10 gm. nitrogen/24 hours/1.73 sq.m. Nitrogen losses of 2 gm. more (our arbitrarily accepted margin of error)—i.e., more than 12 gm. per day—may justifiably be considered due to factors other than simple starvation.

If equilibrium is now postulated when a man is fed 10 gm. nitrogen and 1600 calories/24 hours/1.73 sq.m. (on which we have considerable data showing it to be approximately correct, within 2 gm.) and 10 gm. deficit postulated with complete starvation, these points may be joined and a hypothetical graph made (Fig. I). Expected nitrogen losses per unit surface area may thus be assumed for a given dietary intake where the ratio of protein nitrogen to calories is 6.25 gm. nitrogen: 1000 calories. Such data should be actually obtained experimentally for healthy patients at bed rest and would serve a very useful purpose. For the present, however, and until such accurate data are available, it is of interest to compare the observations on our injured patients with our hypothetically calculated line or normograph.*

Table I gives the figures for nitrogen balance in 6 fracture patients, expressed in terms of an average man (i.e., 1.73 sq.m. surface area) per 24 hours, during equivalent periods after injury. Table II contains similar data for operated cases. The nitrogen balances expected by "normographic" prediction for that dietary level are found in the last column of each table.

One is impressed by the fact that, with widely varying protein intake per unit surface area, these fracture patients exhibited nitrogen losses of a very similar order of magnitude during the period which includes the maximum protein catabolism (from the point of beginning observation through day 13).

Equally significant is the observation that all negative nitrogen balances are greater than would be expected for dietary reasons alone and this is even more striking for the patients to whom diets higher in protein were fed. These facts are also true of the operated cases, although for a much briefer post-operative time.

* It was very fortuitous that on examining the diets on our fracture and osteotomy cases, the ratio of nitrogen to calories was remarkably constant (vide infra; column 5 in table).

TABLE I

Nitrogen Metabolism in Fracture Cases

NAME	DAYS AFTER FRACTURE	DIET/24 HRS./1.73 SQ.M.			N BALANCE OBSERVED	N BALANCE PREDICTED	SPECIAL THERAPY
		N	Cals.	Gm. N/1000 calories			
		gms.			*gm./24 hr./1.73 sq.m.*	*gm./24 hr./1.73 sq.m.*	
Wa.	2–13	9.52	1497	6.48	−9.98	−0.48	
Wo.	5–13	15.48	2360	6.56	−9.45	+5.48	
Ha.	5–13	10.63	1630	6.53	−7.99	+0.63	Testosterone propri-
Fr.	3–13	15.80	2200	7.18	−7.58	+5.80	onate 25 mg. from
Jo.	3–14	5.95	1244	4.79	−8.60	−4.05	10th to 29th day
Ra.	4–13	14.84	2200	6.75	−5.17	+4.84	
Average	4–13	12.04	1888	6.38	−8.13	+2.04	
Wa.	14–22	8.48	1384	6.15	−8.42	−1.52	
Wo.	14–22	15.25	2270	6.75	−4.54	+5.25	
Ha.	14–22	11.08	1688	6.57	−5.52	+1.08	
Fr.	14–22	16.96	2375	6.85	−1.49	+6.96	Testosterone propri-
Jo.	15–23	6.03	1287	4.70	−3.22	−3.97	onate 25 mg. from
Ra.	14–23	15.30	2168	7.07	−3.12	+5.30	10th to 29th day
Ne.	18–23	9.63	1380	6.99	−3.60	−0.37	
Average	15–22	11.82	1793	6.44	−4.27	+1.82	
Wa.	23–31	11.3	1650	6.85	−1.47	+1.30	
Wo.	23–31	14.98	2340	6.40	−3.15	+4.98	
Ha.	23–31	11.16	1710	6.53	−4.12	+1.16	
Fr.	23–34	16.58	2385	6.95	−1.87	+6.58	Testosterone propri-
Jo.	24–32	5.93	1287	4.62	−3.39	−4.07	onate 25 mg. from
Ra.	24–33	15.85	2450	6.48	±0.00	+5.85	10th to 29th day
Ne.	24–32	8.98	1354	6.65	−3.90	−1.02	
Average	23–32	12.11	1882	6.35	−2.56	+2.11	
Wa.	32–40	14.55	2230	6.53	+0.20	+4.55	
Ha.	32–40	11.17	1648	6.77	−3.26	+1.17	
Jo.	33–41	11.06	1900	5.86	−0.21	+1.06	
Ra.	34–39	15.60	2184	7.15	+2.36	+5.60	
Ne.	33–41	9.67	1483	6.54	−1.93	−0.33	
Average	33–40	12.41	1889	6.57	−0.57	+2.41	

TABLE I—*Continued*

NAME	DAYS AFTER FRACTURE	DIET/24 HRS./1.73 SQ.M.			N BALANCE OBSERVED	N BALANCE PREDICTED	SPECIAL THERAPY
		N	Cals.	Gm. N/1000 calories			
		gms.			gm./24 hr./ 1.73 sq.m.	gm./24 hr./ 1.73 sq.m.	
Wa.	41–52	9.45	1514	6.25	−1.92	−0.55	
Ha.	41–52	15.7	2618	6.00	−0.69	+5.70	
Jo.	42–53	11.86	1930	6.15	−0.37	+1.86	
Ne.	42–52	9.46	1520	6.24	−2.05	−0.54	
Average	41–52	11.62	1895	6.16	−1.26	+1.64	
Wa.	53–61	11.34	1796	6.32	+0.85	+1.34	
Jo.	54–62	10.1	1548	6.53	−0.13	+0.10	
Ne.	53–61	9.67	1472	6.58	−1.19	−0.33	
Average	53–61	10.37	1605	6.48	−0.16	+0.37	
Wa.	62–73	14.2	2264	6.28	+1.66	+4.20	
Jo.	63–74	11.92	1921	6.21	+0.45	+1.92	
Ne.	62–73	9.67	1582	6.13	−0.73	−0.33	
Average	62–73	11.93	1922	6.21	+0.46	+1.93	

Fig. II is a graphic representation of these observations in the fracture cases. Expected nitrogen balances (for the intake) are depicted by the "normographic" line, and actual balances are also plotted. Individual cases are depicted by symbols representing the first two letters of the patients' last names. The average nitrogen balance for all cases during the various periods are charted together in the column labelled "means."

Analysis of the data on nitrogen balance when so charted reveals the following points of interest:

1. The large nitrogen losses previously reported for these patients (1) graphically portrayed. During the period of maximal loss (days 4–13 after fracture) the daily nitrogen balance shows a deficit which averages 9 gm./24 hours/1.73 sq.m. surface area. With the next 4 succeeding 7–8 day periods, periods 2, 3 and 4 move closer to the abscissa, meaning that the average individual came closer to nitrogen equilibrium (had less nitrogen deficit). It was not until the 41–52 day

period after trauma that figures for *all* the patients were back on a point within 2 gm. of nitrogen equilibrium or less.

TABLE II

Nitrogen Metabolism in Operated Cases

NAME	AVER. FOR DAYS POST-OPERATIVE	DIET/24 HRS./1.73 SQ.M.			N BALANCE OBSERVED	N BALANCE PREDICTED
		N	Cals.	Gm. N/1000 cal.		
		gms.			*gm./24 hr./1.73 sq.m.*	*gm./24 hr./1.73 sq.m.*
Ch.	1–10	17.45	1980	8.81	−8.7	+7.45
Je.	1–10	10.9	1625	6.72	−7.94	+0.90
Wh. I.	2–11	13.1	1925	6.81	−3.64	+3.10
Wh. II.	1–11	10.98	1760	6.25	−3.56	+0.98
Wo.	1– 9	11.4	1740	6.55	−4.12	+1.40
Average	1–10	12.77	1806	7.03	−5.59	+2.77
Je.	12–21	20.2	3070	6.58	−0.45	+10.20
Wh. I.	12–18	14.03	2064	6.80	−0.70	+4.03
Wh. II.	12–20	14.42	2200	6.56	−0.07	+4.42
Wo.	10–21	14.82	2266	6.55	+0.95	+4.82
Average	10–21	15.87	2400	6.62	−0.04	+5.87
Je.	22–31	20.18	3070	6.57	+2.30	+10.18
Wh. II.	21–32	20.75	3080	6.75	+3.62	+10.75
Wo.	22–30	14.85	2320	6.41	+1.99	+4.85
Average	22–31	18.59	2823	6.58	+2.64	+8.59
Je.	32–42	24.3	3460	7.03	+4.82	+14.30
Wh. II.	33–44	21.05	3100	6.81	+3.47	+11.05
Average	32–43	22.67	3280	6.92	+4.14	+12.67
Wh. II.	45–56	20.8	2980	6.98	+2.92	+10.80
Wh. II.	57–68	20.5	3050	6.61	+3.06	+10.50
Wh. II.	69–80	20.5	3070	6.68	+2.92	+10.50
Wh. II.	81–95	20.8	3120	6.68	+3.60	+10.80
Average	45–95	20.6	3055	6.74	+3.12	+10.65

2. It may be seen that the nitrogen and caloric intake (though the proportion of nitrogen to calories always remained close to 6.6 gm. per

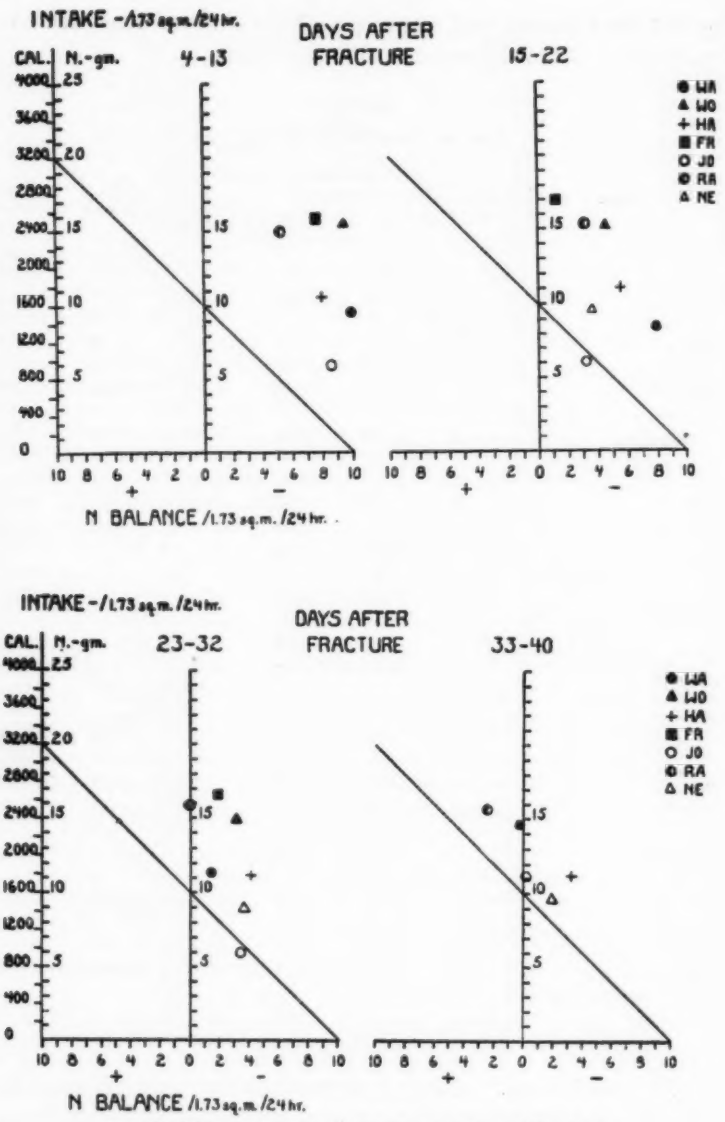

FIG. II. Nitrogen Balance in Relation to Time of Fracture.

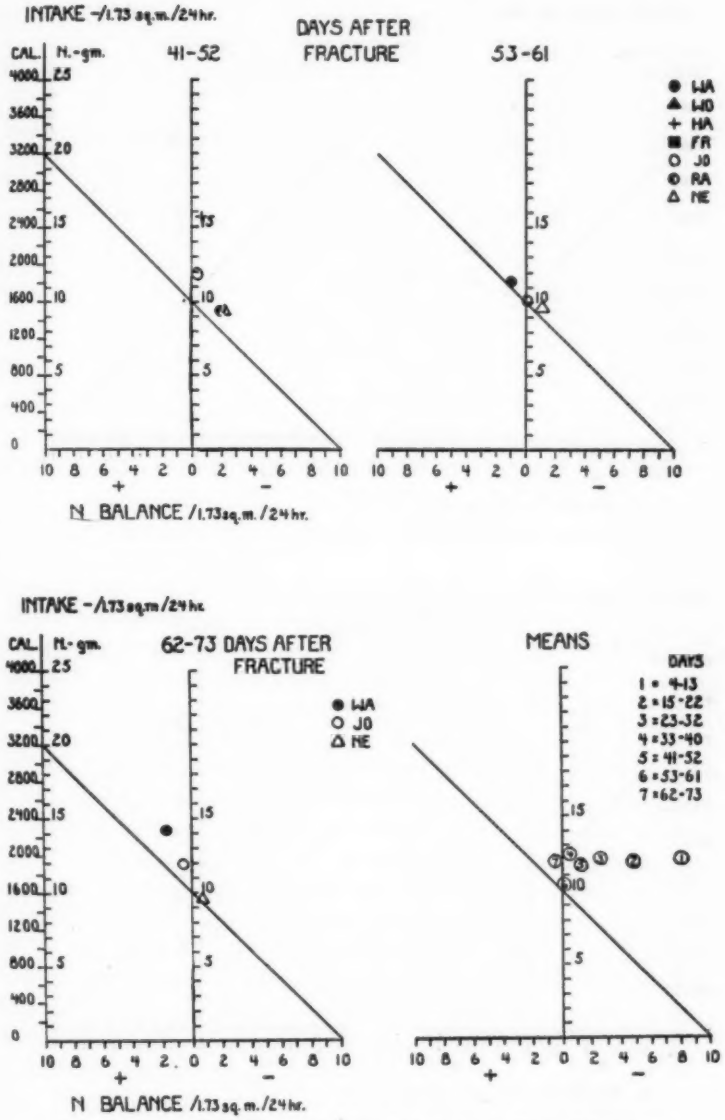

FIG. II (Continued). Nitrogen Balance in Relation to Time of Fracture.

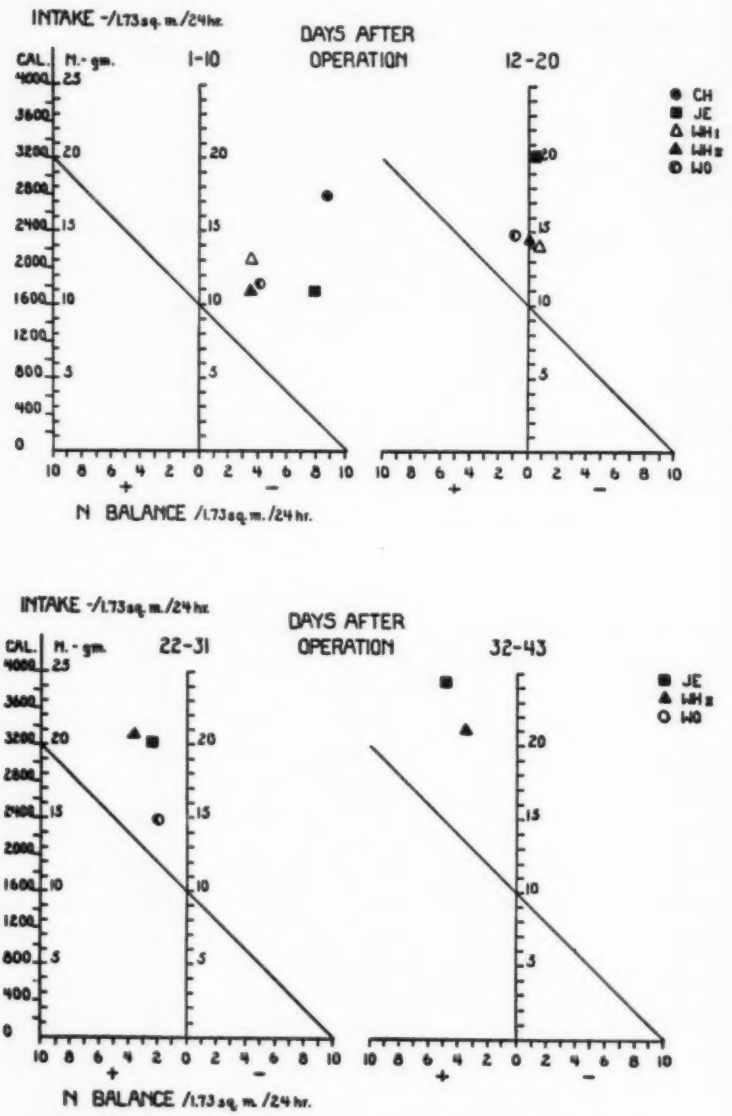

FIG. III. Nitrogen Balance in Relation to Time after Operation.

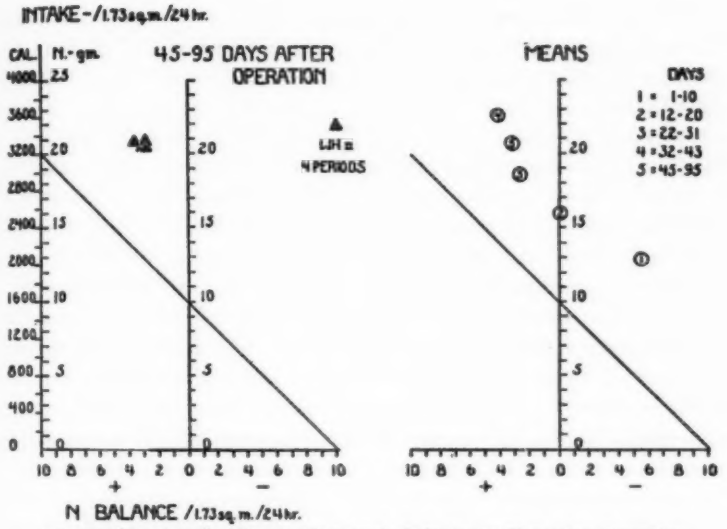

FIG. III (Continued). Nitrogen Balance in Relation to Time after Operation.

1000 calories) of the six patients varied considerably. The patient on the lowest intake—Jo.—ingested for the first 3 charted periods (32 days) approximately 6.6 gm. nitrogen per day and 900 calories per 1.73 sq.m., while the 3 patients on the highest diets—Wo., Fr. and Ra. —ingested 16.5 gm. nitrogen and 2400 calories per 1.73 sq.m. Despite these wide variations in protein and calories administered, the nitrogen deficits (distance from the abscissa) of all the patients are of the same order of magnitude in the first charted period (4–13 days) and nearly so in the second and third charted periods. In other words, although Wo., Fr. and Ra. were each fed, in the first 9-day period, 80 gm. more nitrogen (500 gm. more protein) and 13,500 more calories than were given to Jo., the nitrogen lost from the body protein of each was approximately the same. This extra nitrogen fed was excreted in the urine; each patient who was fed in the first 9-day period 9 gm. more nitrogen per day than Jo. excreted 9 more grams nitrogen per day in the urine.

Analysis of the data on the operated patients when charted (Fig. III) reveals the following:

1. The magnitude of the nitrogen losses per unit of surface area during the height of the protein catabolism varied much more widely from patient to patient than in the fracture cases.

2. Return to nitrogen equilibrium occurred much sooner, for in the second period charted (12–20 days post-operative) all of the patients were again in nitrogen balance (i.e., their "marks" are back on the abscissa).

How soon these patients return to "normographic" nitrogen metabolism (i.e., when the increased tendency to destroy protein has ceased) is not clear, for we have no data with which to plot even a hypothetical graph for expected nitrogen balance in patients at bed rest fed so as to be in positive balance. And, after the first 10-day period, all our operative cases which were followed were in positive nitrogen balance.

3. However, a comparison of the data obtained during the first 10 days postoperative on Je. and Ch., who had identical operative procedures and were of the same age, size and body build, is of considerable interest. After operation Ch. had forced tube feeding with amino acids* and carbohydrate supplements, whereas Je. was treated in the usual manner with glucose and saline for the first 24 hours and thereafter received the small amounts dictated by his appetite. Over the 10-day period Ch. received 50 gm. more nitrogen and 8000 more calories than Je., yet the total nitrogen losses sustained by these two patients were identical. The excess nitrogen administered to Ch. was excreted quantitatively in the urine.

DISCUSSION

From the work of Cuthbertson and our own confirmatory studies, one gains the conviction that, in healthy vigorous male patients with fractures, there is set up, in response to the trauma, a reaction which results in vigorous protein metabolism with losses to the organism *of the nitrogenous portion* of large amounts of body protein. This dynamic process seems to diminish progressively during normal convalescence and to be of much shorter duration after osteotomy than after fracture (1). At the height of the activity of this reaction ("protein catabolic process") the usual effect of increasing the intake of highest quality protein and calories—namely, conservation and storage —is not detectable. It has been pointed out above that, during this

* Amigen and Nutramigen, kindly furnished through the courtesy of Mead Johnson & Co.

period of maximal protein catabolism, a fracture patient on a low protein, low calorie diet (6.5 gm. nitrogen and 900 calories per 1.73 sq.m. surface area) lost no more body nitrogen than did similar patients on higher nitrogen and caloric diets (up to 15 gm. nitrogen with 2400 calories per 1.73 sq.m. surface area). The patients' protein metabolism seemed to be "set" at a point considerably removed from the usual or "normographic" pattern for bed rest, and at this point diet—at least in so far as ingested increments of high quality protein food and total available calories are concerned—did not spare the utilization of endogenous or body protein. The same was found true where added moieties of nitrogen as amino acids were administered by stomach tube to Ch. (operative case). The feeding of more than the minimal nitrogen used in these cases (6.5 gm. nitrogen with 900 calories per unit surface area) was found to put the protein metabolism farther and farther off the "normographic" line but to influence little or none the overall nitrogen balance of the patient. The type of reaction here met seems to demand of the body that a certain amount of endogenous protein be catabolized; and if additional protein, beyond a minimum perhaps, is fed, it is deaminized without serving any sparing effect *on the body nitrogen stores* whatever. It is not meant to imply that, with administration of nitrogen moieties much larger than were used in these experiments, one might not exert such a "head of pressure" that body protein stores might be spared or even nitrogen equilibrium be effected. It is our opinion, however, that to effect such a result, parenteral administration of nitrogen would have to be carried out; for patients of this type under our observation cannot or will not eat more than limited amounts during the early periods of their convalescence. Furthermore, the use of tube feeding, in vigorous patients of the type under discussion, has been accompanied by so much annoyance and discomfort to the patients, with resulting antagonism and animosity, that we have abandoned the method. The wisdom of administering parenterally large amounts of utilizable nitrogen at such times to such patients (whether as plasma or amino acids) will have to wait until it is known (1) whether the protein catabolism process is helpful or harmful to the injured organism and (2) whether by administering large amounts of protein or protein products at this stage, one enhances or prolongs the protein catabolism process.

As the protein catabolism wanes and the patient's protein

metabolism approaches closer to the "normographic pattern," it is clear that the amount of ingested protein influences more and more the overall nitrogen balance in the usual manner—i.e., higher protein moieties and calories tend to spare body protein and the effect is toward more positive nitrogen balance. At such points in the convalescence it seems clear that, other things being equal, the sparing of further body protein losses and the restoration of already sustained losses, must be advantageous to the organism, and high protein and caloric diets would be indicated.

The *nature* and *mechanism* of this protein catabolism process, which is demonstrated in these injured, previously healthy and vigorous individuals, is at the moment unknown. It waxes and wanes ("ebb and flow" of Cuthbertson) and, at its height, demands of the organism a certain amount of its endogenous protein material regardless of whether or not rather large amounts of extraneous protein material are provided. It is certainly unlike the reaction in starvation, in which the expenditure of endogenous protein stores may be readily suspended by provision of either adequate protein or total calories. Nor does it resemble hyperthyroidism in which condition adequate caloric administration reduces the need for protein to minimal amounts (6).

Infection seems to increase the protein catabolism process under discussion (1). The only patient in this group with more than minimal infection was Wa. who developed an abscess in the thigh muscles of the injured side during period 2 (15–22 days after injury). During the period of active infection, with fever up to 102°–103°, his protein metabolism falls farther to the right of the abscissa in the chart than any of the others (see Fig. II). In the subsequent period, after drainage of the abscess and resumption of normal temperature, the graphic point of his protein metabolism falls again in the straight upward line with the others.

The fact that this protein catabolic process occurs after injury in *healthy vigorous* subjects, but not in all subjects, suggests that it may be helpful in some way to the individual. It may be that a patient capable of responding to trauma with a vigorous protein catabolism is a "good surgical risk", whereas a patient unable to respond in this manner is a "poor surgical risk". One patient of ours (not included in this group), who was cachectic from long-standing rheumatoid

arthritis at the time of multiple fractures, failed to show any increase in his protein metabolism whatever. Six grams of nitrogen per day and 900 calories per 1.73 sq.m. were found to keep him in nitrogen equilibrium from the 8th to the 15th day after his injury; and, when plotted on the "normograph", his metabolism fell precisely on the "normographic" line. Likewise Cuthbertson (7) has reported that nitrogen excretion did not rise in injured rats after a period of days on a protein-free diet, whereas in normally fed rats similar injury was followed by well marked losses of nitrogen (8).

It should be mentioned that patient Fr., received testosterone propionate 25 mgm. intramuscularly daily from the 10th to the 29th day (see Fig. II). This medication, known to have nitrogen sparing properties, may have been responsible for the fact that this patient was close to nitrogen equilibrium much sooner than any other member of the fracture group, resembling in this respect the patients subjected to osteotomy.

Although in the height of the protein catabolic phase in these healthy, vigorous fracture and operative cases no sparing action on body protein was observed by higher protein and caloric feeding, it should be reemphasized that we are not in a position to judge as to the possible beneficial or detrimental effect of such a procedure. It may be that portions of the protein molecule other than the nitrogenous may be either used as fuel or stored as glycogen or fat. The coincident movement of potassium and phosphorus, which will be the subject of another report, might serve to throw some light on this question.

SUMMARY

Observations are reported on the influence of the diet on the body nitrogen losses suffered during fracture convalescence and after skeletal operations in vigorous, healthy men. It was found that, at the height of the period of protein breakdown, the ingestion of high protein and caloric diets did not exert any appreciable sparing effect on the losses of nitrogen from the body. As convalescence proceeds, the protein catabolism process gradually wears off and the usual protein metabolism found in patients at bed rest is restored. The possible importance to the organism of this reaction to trauma is discussed.

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A TYPE OF NEURITIS ASSOCIATED WITH MALARIAL FEVER

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A large group of cases with involvement of the nervous system has been encountered in an army General Hospital in which the possibility of a relationship to malarial fever arose. The manifestations were very protean in character and cases showing cranial and peripheral nerve involvement, as well as involvement of the sympathetic nervous system, cerebellum, extrapyramidal system and cerebrum were seen. One type of peripheral neuritis in this group, characterized by pain, hyperesthesia, increased sweating and a feeling of tightness with increase in muscular tone presented a clinical picture seen often in association with malarial fever. It is the purpose of this communication to describe this particular group of cases in detail.

Sensory Manifestations. In the milder of the cases the patient complained of one or more extremities "going to sleep" easily. This complaint was usually volunteered and was frequently the cause of considerable concern on the part of the patient. Some were awakened at night with a feeling of "numbness" and "deadness" in an arm or leg. In others, these symptoms along with a tingling sensation appeared after exercise. In still another group a feeling of puffiness with a tingling or burning sensation was evident at frequent intervals during the day over one particular area, one hand or a foot or with equal frequency over the distribution of a single peripheral nerve. These attacks were fleeting in nature, lasting for only a few seconds. There was often a "drawing" or sensation of "tightness" of the muscles in the same area in which the dysesthesia appeared. These various manifestations made their appearance either concurrently with an acute attack of malarial fever or shortly after treatment was begun. They often continued for many weeks. These mild symptoms were very seldom accompanied by any objective findings on neurological examination, but were in the majority of instances accentuated during subsequent relapses of the malarial fever during which time objective changes appeared in the involved regions. The phenomena described were often bilaterally symmetrical.

In the more severe cases a sharp and continuous pain was present which the patient often compared to a severe toothache. Pain of root distribution was sometimes the first manifestation, and often involved the lower thoracic segments resulting in intense symptoms in the abdominal region. Other nerves which were frequently the site of severe "neuralgia" were the trigeminal, the sciatic and the axillary nerves. Accompanying the pain was the sensation that the region was being pricked with needles, and at the same time a feeling of tightness of the muscles. At this stage there was intense hyperalgesia. Often many nerve roots were involved and the manifestations were bilaterally symmetrical, as illustrated in the following case report:

Case 1. After return from a tropical island this 24 year old white male suddenly developed headache, fever, chilly sensations and joint pains for which he was admitted to the hospital on March 10, 1943. Physical examination, including neurological examination, was normal except for the presence of splenic enlargement. *P. falciparum* was found in the blood smear, and he received routine treatment with quinine and atabrine. He was discharged feeling perfectly well on March 27, 1943 and the following day developed pain around the abdomen and "seemed a little out of his head." The next day he had some diarrhea and the abdominal pain continued. He first saw a medical officer on March 30, 1943 and was told to discontinue his atabrine.

He was readmitted on April 8, 1943 because of persistence of the pain and blood smear again was positive for *P. falciparum*. There was a slight generalized weakness in motor power, but no localized loss of motor function. The reflexes were all equal and active. Over the distribution of the lower two branches of the trigeminal nerve on each side there was intense hyperalgesia. The same manifestations were present over the distribution of the 8th to the 12th thoracic nerves bilaterally. There was also hyperalgesia of glove and stocking distribution involving both hands and both feet. During the following two weeks the hyperalgesia gradually diminished, and the involved areas became definitely hypalgesic. This persisted, and was still present when he was examined three months later.

In other cases subjective discomfort was almost entirely absent or of only very short duration, and the main complaint was of diminished sensation which was often not noticed for several weeks after the acute attack of malarial fever. The feet and hands were frequently involved with hypalgesia and hypesthesia of varying degrees of severity. The distribution was usually that of a posterior root or a peripheral nerve. There was a predilection for the lateral femoral cutaneous nerve and the lower branch of the trigeminal nerve. A case of this type is illustrated by the following history:

Case 2. This 30 year old white male went to a tropical island June 25, 1942, and on November 19, 1942 had his first attack of malarial fever. December 9, 1942 he had his first relapse and two days later, after the temperature had returned to normal, he discovered on awakening that his left leg felt "as though it was asleep." There was a large area of numbness over the skin on the lateral aspect of the left thigh. This persisted and the symptoms were more intense with a subsequent relapse of his malarial fever on March 5, 1943. *P. vivax* was demonstrated in the blood during each of these acute attacks of fever. When examined April 25, 1943 after his third relapse of malaria there was almost complete loss of sensation over the distribution of the lateral femoral cutaneous nerve. The remainder of the neurological examination was normal. During the following three weeks there was no change in the findings, but no subsequent examinations were possible.

Motor Manifestations. During the periods of subjective disturbance described above involuntary muscular movements were occasionally observed which appeared to be fascicular in type. The sensation of "drawing up" was, in the severe cases, accompanied by actual contraction of the involved muscles with the assumption of a characteristic position of the extremity. It occurred most frequently in the flexors of the forearm and fingers, but was also seen in the lower extremity. Of twelve cases with this finding the manifestations were bilaterally symmetrical in eleven. There was no evidence of tetany. The administration of calcium, intravenous saline, and oxygen were without effect, and rebreathing caused no alteration. The contraction was sometimes present for only a few days during the acute attack but in most instances persisted for a period of weeks. It was at times so great that the affected muscles could not be straightened voluntarily, and passively only when considerable pressure was exerted. The attempt at passive movement usually produced considerable pain and increased the subjective sensations. Hyperalgesia always accompanied these motor changes. The following history illustrates a case of this type:

Case 3. This 23 year old white male first went to a tropical island December 28, 1942. He had several attacks of malarial fever and one week after the onset of the third attack on March 18, 1943 he complained of numbness and tingling in the fingers of both hands. His hands felt weak, but there was a sensation of tightness and the fingers tended to "draw up." It was painful to stretch them. These manifestations persisted for about one week and gradually subsided. On May 21, 1943 he was admitted to the hospital because of a recurrent attack of malarial fever, and one week later the same symptoms reappeared, but were more severe

and persisted. *P. vivax* was demonstrated in the blood with each attack of malarial fever.

When the patient was examined on May 28, 1943 the fingers of both hands were drawn up in flexion. They could be extended but not without the production of severe pain. There was increased sweating of both hands, which were warm and pink. There was intense hyperalgesia of the skin over both hands and all of the fingers. The deep reflexes were equal in both arms, and slightly hypoactive. Weakness of the muscles of both arms was observed, particularly of the distal portions. It was difficult to tell how much of this weakness was due to the pain present. When the portion of the sympathetic chain supplying the right arm was blocked with procaine, the paresthesias diminished and extension of the fingers was less painful for a period of twenty minutes. During the subsequent two months he was maintained on suppressive treatment for the malarial fever and the manifestations described gradually subsided.

Vasomotor Manifestations. In the milder case no obvious changes were noted. In the more severe ones the involved areas were usually cool, even when exposed in a warm room, and the skin had a blotchy cyanotic appearance. Profuse sweating was a common finding and sometimes continued over a period of many weeks. In a few cases it was confined to the distribution of a single peripheral nerve, most frequently the ulnar. Such an area would be continually covered with large beads of perspiration even in a cool environment.

Type of Malaria, Age Incidence, Time of Onset. The association of these "irritative" phenomena: hyperalgesia, hyperhidrosis and increase in muscle tone with actual contraction occurring in bilaterally symmetrical areas, usually the forearm and hand, presented a very characteristic picture which was seen in its complete form in sixteen cases. In a number of additional milder cases subjective manifestations only were present and were almost entirely sensory in type. In a consecutive series of 100 cases of malarial fever admitted to this hospital, 18 per cent had symptoms of this milder type alone, with no objective findings on neurological examination. Because of the fact that many of these cases with neurological manifestations of the type described would pass unnoticed unless a very careful history and complete neurological examinations were done, no accurate figures on their incidence can be given. Of fifty patients, about whom complete information was available, including the sixteen severe ones mentioned above, forty-nine had a recurrent type of malarial fever due to *P. vivax* at the time the neurological findings became evident. In one

the infection was due to *P. falciparum* and it is quite possible that in others earlier attacks may have been due to a mixed infection.

All of the patients were white males and the age groups were as follows: 20–25, 24 patients; 26–30, 16 patients; 31–35, 6 patients; 36–40, 3 patients; 41–45, 1 patient. Of interest was the number of attacks of malaria the patient had had when the nervous system involvement was first noted: during first attack or the period of suppressive treatment just prior to the first attack, 19 subjects; with second attack, 16 subjects; third attack, 5 subjects; fourth attack, 5 subjects; fifth attack, 5 subjects. There was considerable variation in the time of onset of the first symptoms of the neurological involvement in relation to the febrile paroxysm. In nine cases it was during the suppressive treatment a few days prior to the onset of active malarial fever; in twenty-four during the first week following the onset of active malarial fever; in twelve during the second week and in five during the third week.

DISCUSSION

A bizarre and extensive series of abnormalities in the function of the nervous system during the course of malarial fever has been seen in this hospital. In the mild cases subjective manifestations of a fairly constant pattern were evident. One or more of the extremities "went to sleep" easily, and was the seat of frequent attacks of numbness and tingling. In some instances there was a mild degree of hypalgesia and hypesthesia over the distribution of a peripheral nerve or a posterior root. These minor changes usually increased in extent and severity during subsequent acute attacks of malarial fever.

The most characteristic type of involvement was in the severer cases in which "irritative" phenomena were predominant. The onset was with sharp or stinging pain in the involved region which was followed by a sensation of "cramping" or "drawing" in the muscles. The flexor surfaces of the forearms and hands were usually involved. Hyperalgesia as well as increased sweating was present, and there was some flexion contraction of the muscles of the involved areas which could be passively reduced, but not without precipitating a great deal of tingling and pain.

Typhus fever may cause nervous system manifestations, but in no instance in this series of cases was the clinical picture of typhus fever present, and in twenty cases in which agglutination tests with proteus Oxk and Ox19 were done all were negative. In certain instances the question of vitamin deficiency arose but none of the associated changes which one would expect to find in such an event were present. Most of the patients had been on an adequate diet as far as the B complex was concerned in the few weeks prior to the development of the neurological changes. Many of the patients had a mild hookworm infection with a few ova of *Necator Americanus* in the stools. In none, however, was the infestation heavy enough to produce any symptoms.

The manifestations described in this communication are not only related to the acute attack of malarial fever, but may develop during the latent phase of the disease when the patient is on suppressive treatment. All of these patients had mild recurrent attacks of malarial fever, lasting for only a few days, and separated by a period of weeks or months during which time they felt well and were generally taking suppressive treatment. Some had lost a moderate amount of weight, but there was no cachexia, severe anemia, or great splenomegaly. In no instance was the picture of so-called chronic malaria present.

From the pathological changes which have been described (cf. Anderson, 1927) it is probable that a vascular basis exists as the cause of nervous system manifestations in malaria. This fits well with the variability of the site of the neurological abnormalities, and also affords a possible explanation for the high incidence of irritative phenomena such as the hyperalgesia, pain, and muscle spasm which have been described above. Lewis and Pochin (1937) have shown that with continued asphyxia, as the response of the skin to touch becomes lost, the intensity of the pain response increases. This more intense and diffuse response to peripheral pain stimuli may be due to an initial irritability preceding the loss of function. The asphyxia which results from partial blocking of the blood supply to a portion of the nervous system may be supposed to cause a transient lowering of the threshold of excitability of the affected nerve fibers, and give rise to the spontaneous discharge of impulses as described by Lehmann (1937) in the cat. With a greater degree of obstruction to the blood supply, loss of function ensues.

SUMMARY

1. A series of cases of malaria with manifestations of nervous system involvement has been described.

2. The typical clinical picture was one in which "irritative" phenomena were present with sharp or stinging pain in the distribution of a peripheral nerve, followed by a sensation of "drawing" in the muscles with actual muscle contraction, intense hyperalgesia, and increased sweating. In the milder cases the manifestations were subjective in nature with transient attacks of numbness and tingling. With recurrent attacks of malarial fever the nervous symptoms increased.

3. In the majority of the cases the attack with which the neurological changes were associated was due to *P. vivax*, though it is possible that there was a mixed malarial infection earlier.

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THE TREATMENT OF PRIMARY AND SECONDARY YAWS WITH PENICILLIN. A PRELIMINARY REPORT

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INTRODUCTION

Recent laboratory and clinical investigations have produced findings which suggest strongly the potential value of penicillin in the treatment of diseases caused by spirochaetes and closely allied organisms. Mahoney, Arnold and Harris (1) treated four cases of early syphilis with good clinical results. Bloomfield, Rantz and Kirby (2) reported similar success in a series of seven cases. In both groups of patients, lesions showing treponemata on darkfield examination prior to treatment were free of these organisms in seven to fourteen hours after the initiation of therapy with penicillin, and healing of the lesions was accomplished within two weeks. The dose of penicillin employed in the treatment of these cases was large, being of the order of magnitude of 1,000,000 units. Recently, the efficacy of penicillin in the treatment of relapsing fever caused by Borrelia novyi in mice was demonstrated by Heilman and Herrell (3) and by Augustine, Weinman and McAllister (4) and in a subsequent report the former workers (5) have shown similar good results in the treatment of experimental Weil's disease in guinea pigs. Because of these findings and because of the availability of cases of yaws in this area, we have felt it desirable to investigate the effect of penicillin upon infections caused by *Treponema pertenue*.

PLAN OF STUDY AND TREATMENT

Cases of active primary and secondary yaws were selected for treatment if darkfield examination of material from the cutaneous lesions revealed spirochaetes morphologically identical with *Treponema pertenue*. Every effort was made to obtain cases with no history of previous arsenical therapy, and to date eleven patients fulfilling this criterion have been treated with penicillin. In addition, because of the scarcity of clinical material at the beginning of the investigation,

six patients with active yaws and a history of clinical relapse following previous chemotherapy were admitted for study. Sixteen of the seventeen cases treated had a positive serum Kahn flocculation test prior to the institution of penicillin treatment. The one case with a negative serum Kahn reaction (case # 1) had had previous arsenotherapy.

All cases treated with penicillin were admitted to the wards of a British Colonial Service hospital for observation during and after the period of treatment. The total dosage of penicillin employed was set arbitrarily at approximately 500,000 units. The usual schedule of administration was 15,000 units of penicillin intramuscularly every four hours day and night for five to six days. The drug solution was made daily by dissolving the dry powder in enough sterile normal saline to produce a concentration of 10,000 units of penicillin per cc. Because of possible deterioration of the drug in transit overseas, the bacteriostatic effect of various lots of penicillin against a laboratory strain of Staphylococcus aureus was measured and found to equal the effect of a potent preparation described by Keefer and Rammelkamp (6). No other treatment, systemic or local, was employed during the period of penicillin therapy. Open, draining, cutaneous lesions were covered with a vaseline gauze dressing to prevent trauma and the recurrence of bacterial invasion. Lesions covered with a dry eschar were not dressed. Darkfield examinations of material from the lesions in which T. pertenue was demonstrated before treatment were repeated sixteen and forty hours after the institution of therapy. Titred serum Kahn reactions were determined during and after hospitalization at weekly intervals, and the patients were reexamined at weekly intervals following discharge from the wards.

The effect of penicillin upon the clinical course of active primary and secondary yaws is described in the histories of the typical cases given below and in Tables I and II.

Case # 2. J. K., a fifteen year old Fijian boy, was admitted to the clinic on April 19, 1944, complaining of sores on his skin. A year previously he had developed below his left knee a small ulcerative lesion that had increased gradually in size during the next six months. "Several months" before entry new lesions had appeared on both legs, and two weeks before admission another lesion had

developed at the mucocutaneous junction of the left external naris. The patient gave no history of any treatment during his illness.

Physical examination showed a well nourished, well developed Fijian male who presented the typical appearance of moderately severe secondary yaws. There was a large weeping granuloma below the left knee and on both legs were found numerous elevated lesions covered with dirty, yellowish, lobulated eschars. There was a small granuloma at the mucocutaneous junction of the left external naris. Superficial circinate lesions involving the epithelium of both palms and soles were also present. There was moderate enlargement of the epitrochlear and femoral lymph nodes. The remainder of the physical examination was not remarkable. Darkfield examination of material from the lesion below the left knee showed moderate numbers of spirochaetes morphologically identical with *T. pertenue*. The serum Kahn test was positive, titre twelve units.

The patient was hospitalized and given an initial dose of 25,000 units of penicillin intravenously. Thereafter, at four hourly intervals he received 15,000 units of penicillin intramuscularly until a total amount of 460,000 units had been administered. After sixteen hours of treatment, darkfield examination of material from the lesion below the left knee revealed no treponemata, and the absence of these organisms from the lesions was confirmed by darkfield examination after forty hours of treatment. At this time all of the lesions appeared improved and less oedematous, and evidence of secondary infection was less pronounced. Twenty-four hours later, epithelialization of the smaller lesions was noted, and on the eighth day after the start of therapy all of the lesions were completely epithelialized. The patient has been followed at weekly intervals for seven weeks since the beginning of treatment and he has remained well. The course of his titred serum Kahn reaction can be seen in Table II.

Case #9. M. L., a four and a half year old Fijian girl, was admitted to the outpatient department May 6, 1944, complaining of a sore on the right second toe. The lesion had appeared a week previously as a small ulceration which had been covered soon by a thick yellowish crust. The patient's mother recognized the lesion to be a yaw and brought the patient to the hospital. There was no history of therapy prior to admission.

Physical examination showed a well developed, fairly well nourished Fijian female who did not appear ill. On the right second toe there was a large circular solitary yaw about eighteen mm. in diameter which involved the dorsal and medial aspects of the digit. The periphery of the lesion was covered with a dirty, yellowish eschar which overlay pale, oedematous granulations. The central portion of the lesion was depressed and covered with a greyish eschar. The epitrochlear glands were slightly enlarged. The remainder of the physical examination showed nothing noteworthy. Darkfield examination of material from the lesion on the right second toe revealed numerous spirochaetes morphologically identical with *T. pertenue*. The serum Kahn reaction was positive, titre one hundred twenty units.

The patient was hospitalized and treated with penicillin. She received 15,000

units of penicillin intramuscularly at four hourly intervals until a total of 450,000 units had been injected. Sixteen hours after the start of treatment, darkfield examination of material from the primary yaw showed no treponemata and this finding was repeated at forty hours. At this time the oedema of the granulations had subsided and the eschar had begun to separate. Thereafter, progress was rapid and the lesion healed completely one week after the start of treatment. Three weeks after the commencement of therapy, the lesion remained well healed. The course of the serum Kahn reaction is recorded in Table II.

Case #16. M. T., a seventeen year old Fijian male, was admitted to the clinic May 24, 1944, complaining of sores on his face, hands and legs. Approximately a month previously, he had developed an ulcerative lesion on his right fifth toe. A week later, numerous other lesions had appeared on the face, hands and legs. Because of the failure of the lesions to improve, the patient came to the hospital. There was no history of treatment prior to admission.

Physical examination showed a well developed, rather thin Fijian male who presented the clinical picture of florid secondary yaws. Over the face, hands and legs there were numerous typical lesions varying in size from one cm. to three cm. in diameter. The palms and soles were involved extensively. The right fifth toe was affected in its entirety and appeared to be infected heavily with secondary bacterial invaders. There was a lesion at the mucocutaneous junction of the right external naris which appeared to involve almost completely mucous membrane. The femoral lymph nodes were markedly enlarged. The remainder of the physical examination was normal. Darkfield examination of material from a lesion on the left hand showed numerous spirochaetes morphologically identical with *T. pertenue*. The serum Kahn reaction was positive, titre one hundred sixty units. X-ray of the right fifth toe showed decreased density of the phalanges.

The patient was treated with penicillin, receiving 15,000 units intramuscularly at four hourly intervals until a total quantity of 450,000 units had been given. From the beginning of treatment the patient's progress was dramatic. Darkfield examinations revealed no spirochaetes after sixteen hours of treatment nor at any time subsequently. At the same time the darkfield examinations became negative, beginning epithelialization of most of the lesions was in evidence. The rate of improvement of the right fifth toe was most striking. On admission the entire toe was involved by the infectious process and it was thought then that the toe might be lost. In three days the oedema and purulent discharge disappeared, and on the fourth day it seemed possible that the toe might heal without surgical intervention. At the end of nine days the toe was covered completely with epithelium and all of the lesions elsewhere were healed. The course of the serum Kahn reaction is shown in Table II.

DISCUSSION

The salient features of seventeen cases of yaws treated with penicillin are presented in Table I. Of this group eleven patients had

TABLE I

Clinical Data on Patients with Yaws Treated with Penicillin

CASE	NAME	AGE	SEX	RACE	TYPE OF YAWS	DURATION OF ILLNESS	SEVERITY OF ILLNESS	PREVIOUS THERAPY	INTERVAL BETWEEN PREVIOUS TREATMENT AND PRESENT ADM.	SERUM KAHN	DARKFIELD BEFORE TREATMENT	DARKFIELD AFTER 16 HRS. OF PENICILLIN TREATMENT	TOTAL PENICILLIN ADMINISTERED	STATE OF SKIN LESIONS 3 WKS. AFTER TREATMENT	PERIOD OF OBSERVATION
no.									*mo.*				*units*		*wks.*
1	V. V.	10	F	Fijian	Secondary	3 months	Moderate	1 arsenic injection	1	Neg.	Pos.	Neg.	280,000	Healed	7
2	J. K.	15	M	Fijian	Secondary	1 year	Moderate	None		Pos.	Pos.	Neg.	470,000	Healed	7
3	L. B.	9	F	½—Fijian ½—Chinese	Secondary	1 year	Severe	3 arsenic injections	1	Pos.	Pos.	Neg.	510,000	Healed	5
4	V. W.	12	F	Fijian	Secondary "Crab"	6 months	Moderate	3 arsenic injections	4	Pos.	Pos.	Neg.	480,000	Healed	6
5	E. S.	1	F	Fijian	Secondary	3 months	Severe	None		Pos.	Pos.	Neg.	420,000	Healed	4
6	A. L.	1	F	Fijian	Secondary	1 month	Severe	None		Pos.	Pos.	Neg.	420,000	Healed	3
7	A. A.	9	F	Fijian	Secondary	1 year	Moderate	3 arsenic injections	1	Pos.	Pos.	Neg.	200,000	Healed	5
8	M. V.	3	F	Fijian	Secondary	7 months	Mild	3 arsenic injections	5	Pos.	Pos.	Neg.	525,000	Healed	5
9	M. L.	4½	F	Fijian	Primary	1 week	Mild	None		Pos.	Pos.	Neg.	480,000	Healed	4
10	K. K.	3	F	Fijian	Secondary	1 month	Moderate	None		Pos.	Pos.	Neg.	540,000	1 lesion not healed	4
11	J. Ka.	4	M	Fijian	Secondary	1 month	Moderate	None		Pos.	Pos.	Neg.	540,000	Healed	3
12	T. V.	7	M	Fijian	Secondary	3 months	Moderate	None		Pos.	Pos.	Neg.	540,000	Healed	4
13	M. R.	5	M	Fijian	Secondary	4 months	Severe	2 bismuth injections	2	Pos.	Pos.	Neg.	450,000	Healed	3
14	N. K.	6	M	Fijian	Secondary	1 year	Moderate	None		Pos.	Pos.	Neg.	450,000	Healed	3
15	P. L.	9	F	½—European ½—Samoan	Primary	3 weeks	Mild	None		Pos.	Pos.	Neg.	450,000	Healed	3
16	M. T.	17	M	Fijian	Secondary	1 month	Severe	None		Pos.	Pos.	Neg.	450,000	Healed	3
17	I. N.	1	M	Fijian	Secondary	2 months	Severe	None		Pos.	Pos	Pos. Neg. after 40 hours	100,000	Healed	3

Course of Serum Kahn Reactions in Patients with Yaws Treated with Penicillin

AME	BEFORE TREAT.	4 DAYS	1 WK.	2 WKS.	3 WKS.	4 WKS.	5 WKS.	6 WKS.	7 WKS.

17	I. N.		M	Fijian	Secondary	2 months	Severe	None		Pos.	Pos	Pos. Neg. after 40 hours	100,000	Healed	3	

Course of Serum Kahn Reactions in Patients with Yaws Treated with Penicillin

no.	NAME	BEFORE TREAT.	4 DAYS	1 WK.	2 WKS.	3 WKS.	4 WKS.	5 WKS.	6 WKS.	7 WKS.
1	V.	Neg.		Neg.		Neg.	Neg.	Neg.	Pos. 4 units	Pos. 4 units
2	. K.	Pos. 12 units	Neg.	Neg.	Pos. 20 units		Pos. 80 units	Pos. 80 units	Pos. 80 units	
3	B.	Pos. 120 units	Pos. 160 units	Pos. 120 units	Pos. 160 units	Pos. 240 units	Pos. 200 units			
4	.	Pos. 20 units	Pos. 20 units		Neg.	Neg.		Pos. 240 units	Pos. 240 units	
5	E. S.	Pos. 4 plus	Pos. 240 units	Pos. 240 units	Pos. 320 units		Pos. 200 units			
6	A. L.	Pos. 4 plus	Pos. 200 units	Pos. 160 units	Pos. 200 units	Pos. 200 units				
7	A. A.	Pos. 4 plus		Pos. 240 units	Pos. 200 units	Pos. 240 units	Pos. 200 units			
8	M. V.	Pos. 2 plus	Pos. 80 units	Pos. 80 units			Pos. 4 units			
9	M. L.	Pos. 120 units		Pos. 160 units	Pos. 40 units	Pos. 40 units				
10	K. K.	Pos. 80 units		Pos. 200 units	Pos. 240 units	Pos. 200 units				
11	J. Ka.	Pos. 160 units		Pos. 40 units	Pos. 20 units					
12	T. V.			Pos. 240 units	Pos. 240 units		Pos. 200 units			
13	M. R.	Pos. 280 units		Pos. 240 units	Pos. 200 units					
14	N. K.	Pos. 4 units		Pos. 4 units	Pos. 4 units	Pos. 40 units				
15	P. L.	Pos. 240 units		Pos. 240 units	Pos. 120 units					
16	M. T.	Pos. 160 units		Pos. 200 units	Pos. 240 units					
17	I. N.	Pos. 240 units		Pos. 240 units	Pos. 240 units					

never received previous therapy, one had been given bismuth and five had been treated with arsenic at some time before the administration of penicillin was begun. In every case, whether or not there had been previous therapy, the lesions had been progressing unfavorably before hospitalization. In every case, also, organisms morphologically identical with *Treponema pertenue* were demonstrated at the original darkfield examination. The darkfield study, repeated sixteen and forty hours after the commencement of treatment with penicillin, showed no treponemata in sixteen patients. In one case a single, non motile *Treponema pertenue* was found after sixteen hours, but none was present at forty and sixty four hours. During these first sixteen hours the dose of penicillin varied from 50,000 to 90,000 units, and all of the lesions showed definite evidence of healing at the end of this period. Thereafter, healing progressed with almost spectacular rapidity. Granulomas and ulcers became dry and clean and were covered soon with a firm eschar. Epithelium grew in from the periphery of the lesions and the crusts separated. Ulcers and granulomas several centimeters in diameter healed often within a week. All of the lesions but one were completely healed within three weeks. This exception was a large, deep ulcer on the right foot of Case # 10. It showed the usual initial improvement, but its epithelialization was impeded by the development of a surrounding ring of fibrous tissue. Treponemata were not demonstrated in the ulcer in five darkfield examinations subsequent to therapy. In the same patient the other numerous lesions healed uneventfully. From the observations noted above, we feel justified in stating that the administration of penicillin causes the *Treponema pertenue* to disappear promptly from the cutaneous lesions of primary and secondary yaws and that it produces rapid and complete healing of the skin manifestations of these stages of the disease.

The course of the serum Kahn reactions is shown in Table II and reveals no significant changes during the period of observation. Obviously this period is too brief to prove conclusive and changes in the Kahn reactions may occur subsequently. In this regard the statement of Chambers (7) concerning the effect of arsenotherapy upon the Kahn reaction in yaws is of interest. "In 411 cases of yaws with Wassermann reaction positive treated with six injections of neo-

arsphenamine the lesions cleared in the usual time but the Wassermann reaction was still positive at the end of six months in 74.56 per cent of these cases; it was positive at the end of one year in 55.03 per cent; at the end of two years in 31.63 per cent of the cases." The clinical importance of a positive serological test in yaws is difficult to evaluate. Because of the apparent rarity of cardio-vascular, central nervous system and other visceral involvment in yaws, a positive serological reaction may have a different significance than in syphilis. As one of the criteria of a complete cure of yaws, however, the serological test should, in the light of present knowledge, become negative and remain so. Our studies of the course of the serum Kahn reaction are being continued.

The optimal dose of penicillin in yaws has not been determined by this investigation. Most of our cases were given a total of 400,000 to 500,000 units of the drug in five days. A dosage of 100,000, 200,000, and 270,000 units of penicillin brought about as prompt and complete healing of the skin lesions as the more vigorous therapy. From a consideration of the results of preliminary studies in the treatment of syphilis with penicillin, it appears that the smaller quantities may be sufficient. We also have no information on the comparative effectiveness of penicillin and the arsenical compounds in the treatment of yaws. Further investigation of these problems is in progress. The study of a large group of cases and a prolonged period of observation will be necessary before they can be solved.

SUMMARY

1. Seventeen cases of primary and secondary yaws from which Treponema pertenue was isolated by darkfield examination have been treated with penicillin.

2. Penicillin caused the disappearance of *Treponema pertenue* from the cutaneous lesions within sixteen hours in sixteen cases and within forty hours in one case.

3. Penicillin therapy brought about complete healing, within three weeks, of all the cutaneous manifestations of yaws with the exception of one lesion which failed to epithelialize because of local scar formation.

4. During the short period of observation penicillin did not affect significantly the serum Kahn reaction in yaws.

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MUMPS WITH PRE-STERNAL EDEMA[1]

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In 1918 Ravdin (1) stated that edema of the soft tissues overlying the sternum was known to occur during the course of epidemic parotitis. He gave no indication as to the frequency with which such edema occurred. In 1943 Barker (2) reported three patients with mumps complicated by pre-sternal edema and Rappaport (3) reported two similar cases. Standard textbooks on contagious diseases fail to list pre-sternal edema as a complication of mumps and in view of its apparent rarity, its occurrence in six percent of patients involved in a recent epidemic is of interest.

In the spring of 1944, five hundred and two patients who were admitted to the station hospital at Fort Benning, Georgia with mumps were examined daily throughout their illness. Of these patients, thirty developed pre-sternal edema. The outbreak at Fort Benning which involved young army inductees from southern rural areas in no way appeared to be of unusual severity.

The onset of the edema in the thirty cases was noted on the average of five and eight-tenths days from the appearance of glandular swelling and lasted on the average of five days. In table 1 are listed the individual patients and the specific glands involved in their disease, together with the time of onset and duration of the edema. From this chart it will be noted that twenty-five of the thirty patients had swelling of one or both of the submaxillary glands at the time the pre-sternal edema became evident, whereas five patients had parotid mumps only. The latter group exhibited mild pitting edema of brief duration. The duration of edema was based on the length of time during which pitting was clearly demonstrable. However, in several

[1] This work was carried out under the direction of the Commission on Measles and Mumps of the Board for the Investigation and Control of Influenza and other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, U. S. Army.

We wish to express our appreciation to Lt. Col. E. Bowie, Regional Hospital, Fort Benning, Georgia, for his suggestions concerning the x-rays of our patients.

patients a slight non-pitting swelling over the sternum persisted for a longer period of time.

TABLE 1

CASE NUMBER	GLANDS INVOLVED AT TIME OF ONSET OF EDEMA	DAY OF DISEASE EDEMA BEGAN	DURATION OF EDEMA
			days
1	Both parotids	7th	4
2	Left parotid; both submaxillary	12th	4
3	Right parotid, right submaxillary	4th	6
4	Both parotids, left submaxillary	4th	4
5	Both parotids, left submaxillary	5th	5
6	Both parotids, right submaxillary	6th	6
7	Both parotids, left submaxillary	6th	5
8	Both parotids, both submaxillary	7th	3
9	Both parotids	6th	2
10	Right parotid	4th	2
11	Both parotids, both submaxillary	5th	4
12	Both parotids, right submaxillary	6th	10
13	Both parotids, left submaxillary	6th	6
14	Right parotid, right submaxillary	7th	6
15	Right parotid, right submaxillary	5th	4
16	Both parotids, left submaxillary	8th	3
17	Both parotids, left submaxillary	3rd	18
18	Right parotid, right submaxillary	9th	4
19	Left parotid, left submaxillary	5th	3
20	Both parotids, both submaxillary	3rd	4
21	Both parotids, right submaxillary	8th	7
22	Left parotid, right submaxillary	5th	8
23	Both parotids, left submaxillary	5th	5
24	Both parotids	5th	2
25	Both parotids, both submaxillary	6th	5
26	Both parotids, both submaxillary	5th	6
27	Both parotids, both submaxillary	5th	5
28	Right parotid, left submaxillary	7th	5
29	Both parotids, both submaxillary	5th	3
30	Right parotid	5th	3

In all patients the edema gave rise to a characteristic pattern. The lower border invariably assumed the shape of a necklace and extended downward to a point ranging between the third interspace and the xiphoid process. Laterally, the edema extended an equal distance on both sides of the sternum, varying from a point three

centimeters from the edge of the sternum to the mid-clavicular line. The symmetry of the edema was constant and was unaffected by the asymmetry of glandular involvement. There appeared to be no

FIG. 1*. C. M. DURING FIRST DAY OF EDEMA

relationship between the severity of the parotitis and the degree of edema.

The edema usually reached its height on the second day after its onset. In only three patients did the skin of the involved area show

* Photographs were made by the Signal Corps, U. S. Army.

any changes; in these three it assumed a dull red hue. There was no engorgement of superficial veins either in the chest or neck. In all

FIG. 2. C. M.: LATERAL FILM TO DEMONSTRATE SWELLING OF PRE-STERNAL SOFT TISSUES

instances the swelling was called to the attention of the patient. Only five patients developed symptoms coincident with the edema; two complained of dysphagia of about twenty-four hours duration, another of hoarseness, and two of tenderness over the sternum when pressure

was applied. With the exception of these five, the remaining patients were asymptomatic as far as the edema was concerned.

FIG. 3. H. B.: PHOTOGRAPH TAKEN ON SECOND DAY OF EDEMA

All of the patients were afebrile at the time of onset of the edema and the course continued afebrile throughout except in those patients who developed a complicating orchitis. The frequency of orchitis

was no greater in the group of thirty patients than in the remaining four hundred and seventy-two patients.

The edema disappeared gradually with the subsidence of the glandular swelling; in no case did it persist following the return to normal

FIG. 4. H. B.: LATERAL FILM DEMONSTRATING PRE-STERNAL EDEMA

of the swollen glands. In several patients, however, it continued at its height despite a rapid decrease in size of the glands.

There was no evidence of involvement of the thyroid gland. X-rays of the chest in both lateral and anterior views at the height of the edema failed to show enlargement of the thymus or other abnormal-

ities of the chest and neck except for the edema of the superficial soft tissues overlying the sternum. In all of the patients the sternal notch was obliterated by edema and in three of the patients the swelling

FIG. 5. H. B.: LATERAL FILM DEMONSTRATING PITTING OF THE EDEMATOUS TISSUES FOLLOWING THE APPLICATION OF PRESSURE

was so marked as to completely obscure the supra- and infra-clavicular spaces.

The white blood counts in these patients differed in no way from counts in patients whose disease was uncomplicated by pre-sternal

edema. There were no positive heterophile antibody tests in this group.

FIG. 6. M. C. D.: LATERAL FILM DEMONSTRATING PRE-STERNAL EDEMA

The following three cases were chosen as representative of the group of patients exhibiting pre-sternal edema:

C. M. developed mumps involving both parotids and the left submaxillary gland one day before admission to the hospital. On the fifth day of his disease pitting edema over the sternum was first noted. The edema lasted five days during the course of which the glands subsided rapidly but were still slightly en-

larged at the time the edema had entirely disappeared. The patient had daily temperature elevations for the first three hospital days but remained afebrile thereafter.

H. B. developed mumps involving the left parotid gland two days before admission to the hospital. On the fifth day of the disease the right parotid became swollen and on the seventh day the right submaxillary became enlarged. On the eighth day of the disease he first showed pitting edema over the sternum extending down to the third interspace. He complained of dysphagia of about twenty-four hours duration. The pitting edema persisted for seven days, at the end of which time the right submaxillary and left parotid glands were still slightly enlarged.

M. C. D. developed mumps involving the right parotid gland one day before admission. On the sixth day of the disease the right submaxillary became swollen and on the seventh day of the disease pitting edema made its appearance over the sternum, extending down to the fourth interspace. On the following day the skin over the edematous area became dull red in color and the edema had extended laterally almost to the nipple line on both sides of the sternum. The edema lasted six days.

The etiology of pre-sternal edema accompanying mumps is uncertain. The development of the edema shortly after involvement of the submaxillary glands in so many of the cases appears to favor lymphatic obstruction as the underlying cause. Ravdin described one patient with pre-sternal edema who was shown to have an enlarged thymus shadow on x-ray and attributed the edema to obstruction of the lymph supply by the inflamed thymus. We were unable to demonstrate any abnormalities of the thymus in our patients. Both Barker and Rappaport favor obstruction of the lymphatics by the swollen salivary glands as the cause of the edema.

SUMMARY

1. That pre-sternal edema is not a rare complication of mumps is indicated by its occurrence in thirty patients during a recent outbreak.

2. In all cases the edematous tissues pitted easily; this fact was verified by means of lateral soft tissue x-ray films.

3. In twenty-five of the patients the edema began shortly after the involvement of the submaxillary glands. Five patients had parotid swelling only but in these five the edema was mild and of brief duration. The average duration of the edema in the thirty patients was five days.

4. It is felt that obstruction to lymphatic drainage by the swollen glands is responsible for the pre-sternal edema.

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